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EXAMINER
ZITOMER, STEPHANIE W

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1634	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/834,109	Applicant(s) SEGAL ET AL.	
	Examiner Stephanie Zitomer	Art Unit 1634	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Objection under 37 CFR 1.75(c): Improper claim dependency

1. Claim 21 is objected to under 37 CFR 1.75(c), as being of improper dependent form because a multiple dependent claim must refer to the multiple other claims in the alternative only. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 21 improperly depends from two claims without being in the alternative.

Rejection under 35 U.S.C. 101: Lack of specific asserted utility

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 1-22 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility. The claims are broadly drawn to nucleic acid molecules comprising a "biological effector sequence" and methods of performing gene therapy in humans which has not been shown to be an operable and, therefore useful, process. The specification generically describes use of the claimed nucleic acid molecules in methods of "introducing a biological effector sequence into a cell" as "including methods of administration of a composition...to an organism" which may be prokaryotic or eukaryotic and includes humans (page 24). However, no specific utility for the claimed invention nucleic acid molecules or methods is disclosed, i.e., delivery of a specific biological effector to a specific organism by a specific route and which results in or would reasonably have been expected by one of skill in the art to result in a specific therapeutic effect is described.

Rejection under 35 U.S.C. 112, *first paragraph*: Lack of enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-22 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. There is no working example or description or even a prophetic example of the claimed aptamer covalently linked to a nucleic acid sequence comprising a "biological effector sequence" which, when introduced into an organism by the claimed invention method, effects a specific biological reaction. Examples of "biological effector sequences" include coding and antisense nucleic acids, nucleic acid enzymes and regulatory nucleic acids (page 14, first paragraph, followed by lists of prospective effector sequences). Working examples (pages 30-35) are prophetic with the exception of Example 6 in which antisense effector sequences were shown to inhibit expression of Enhanced Green Fluorescent Protein to a greater degree when conjugated to a human L-selectin aptamer than the aptamer alone. The specification is primarily directed to gene therapy of animals including humans (pages 27-29). However, at the time the application was filed, the prior art taught that gene therapy and antisense therapy were inoperative at worst and unpredictable at best. For example, Orkin et al. (1995) reviewed the state of the gene therapy art and reported that, among other problems, "[e]fficacy has not been established for any gene therapy protocol". Notably, in this regard, the specification describes dosage and administration in generalities (pages 28-29) but fails to provide any specific protocol for performing the claimed invention gene therapy methods. The Orkin et al. report also cited "the low frequency of gene delivery to target cells and the lack of definable biochemical or clinical endpoints". Notably, in this regard, the specification fails to identify any biochemical or clinical endpoints of the claimed invention methods. Administration of antisense oligonucleotides has been shown to have unexpected effects as reported in *Science* (Gura 1995). In one example wherein inhibition of B cell activity in culture was attempted the antisense oligonucleotides instead increased B cell activity. This report also cited side effects in animals administered antisense oligonucleotides including death in some instances. While the level of skill in the molecular biology art was high at the time of the claimed invention, Ph.D. or higher, the level of unpredictability was also high as demonstrated by the cited references. Absent the required teaching and/or guidance in the

specification, it is clear that the skilled practitioner in the art would have experienced undue experimentation in attempting to practice the claimed invention methods of "introducing a biological effector sequence into a cell" in an organism and "administering said molecule to an organism" and that the disclosure is nothing more than an invitation to experiment. As the Courts have stated,

> A specification must be more than an invitation to experiment, i.e., applicant may not require persons skilled in the art to perform undue experimentation to achieve a successful result. See *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1933); *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Rejections under 35 U.S.C. 112, second paragraph: Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 3-6 and 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 3-6 lack antecedent basis for "said nucleic acid molecule" because it is unclear whether the "molecule" is the first, second or third nucleic acid molecule of claims 1-4. It is suggested to clarify by inserting --first-- or --second-- or --third-- after "said" in claims 3 and 4.

(b) Claim 10 is confusing because

(c) Claims 19-22 are indefinite in being *non sequitur* to claims 1 or 2 from which the former depend. Claims 1 and 2 recite a molecule comprising a "biological effector sequence" and an "aptamer". It is suggested to amend claims 19-22 to indicate what, if any, relationship the "aptamer" has to the method of "introducing".

(d) Claims 19-22 are indefinite in lacking positive, active method steps for "introducing...into a cell" because "contacting" and "administering" are not method steps of "introducing...<u>into</u>" (emphasis added). Method claims need not recite all operating details

but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter the claims encompass as well as make clear the subject matter from which others would be precluded. *Ex parte Erlich*, 3 USPQ2d 1011 at 6. It is suggested to amend the claims to recite positive step(s) of getting the molecule into the cell and to the cell in an organism.

(e) Claim 20 is confusing because "organism" in line 2 is *non sequitur* to "cell" in line 1. It is unclear how administering a molecule to an organism relates to introducing a sequence into a cell. It is suggested to clarify the relationship between "cell" and "organism".

(f) Claim 22 lacks antecedent basis for "an organism" in line 4. It is suggested to replace "an" with --the-- to provide direct reference to the antecedent "organism" in the preamble.

Rejection under 35 U.S.C. 102(b): Anticipation

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 3, 5, 7 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Gold et al. (5,270,163). Regarding claims 1, 3, 5 and 7, the claimed invention nucleic acid molecule comprising an aptamer linked to a nucleic acid sequence comprising a biological effector sequence wherein the nucleic acid is DNA or RNA and wherein a third nucleic acid sequence comprising a different aptamer may be linked or hybridized to the nucleic acid molecule is disclosed at column 7, lines 12-42 with column 9, lines 15-33, column 11, lines 6-24 and column 13, lines 32-35. The composition of claim 16 comprising the claimed invention nucleic acid molecule of claim 1 and a biologically acceptable carrier is disclosed at column 5, lines 27-31.

Rejections under 35 U.S.C. 102(e): Anticipation

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

7. Claims 1, 3, 5, 7, 8, 12-14 and 16-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Burke et al. (5,637,459) in view of Gold et al. (5,270,163). Regarding claims 1 and 7, the claimed invention nucleic acid molecule comprising an aptamer covalently linked to a second nucleic acid sequence comprising a biological effector sequence is disclosed at column 15, lines 42-43 (Example 1). Gold et al. is cited to show that the HIV-1 reverse transcriptase aptamers of Burke et al. are biological effectors because they inhibit the enzyme activity (Gold et al., column 42, lines 42-53) and that the "nucleic acid" encompasses DNA and RNA (column 13, lines 32-40). The claimed invention nucleic acid molecule described above is disclosed by Burke et al. also at column 17, lines 14-25 (Example 3) as a chimeric nucleic acid molecule that effects acetyl CoA transfer. Regarding claims 3 and 5, the claimed invention nucleic acid molecule further comprising a third nucleic acid sequence which is a different aptamer covalently linked thereto is disclosed at column 19, lines 1-4 (Example 6). Regarding claim 8, the claimed invention nucleic acid molecule wherein the biological effector sequence encodes a polynucleotide is disclosed at column 17, lines 17-19 as a DNA molecule that encodes an RNA transcript. Regarding claim 12, the claimed invention nucleic acid molecule wherein the biological effector sequence comprises a nucleic acid enzyme is disclosed at column 18, lines 42-49 (Example 18) as a chimeric nucleic acid molecule comprising a ribozyme. Regarding claim 13, a nucleic acid comprising a template for assembly of the claimed invention nucleic acid molecule is disclosed at column 17, lines 17-19. Regarding claims 14 and 16-18, a cloning vector comprising the claimed invention nucleic acid molecule, a composition comprising an admixture of the claimed invention nucleic acid molecule, a cell that bears a target for the aptamer thereof and a cell transfected with the claimed invention nucleic acid molecule are disclosed at column 17, lines 31-36 wherein the cells and vectors are in an admixture prior to transfection.

8. Claims 1, 2, 4, 6 and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Cubicciotti (5,656,739). Regarding claim 1, the claimed invention nucleic acid molecule comprising an aptamer covalently linked to a second nucleic acid sequence comprising a biological effector sequence is disclosed at column 27, claim 1. Regarding claim 2, the embodiment wherein the first and second nucleic acid sequences are linked via Watson-Crick base pairing is disclosed at column 28, claim 8. Regarding claims 4 and 6, the claimed invention nucleic acid molecule further comprising a third nucleic acid sequence which is a different aptamer linked thereto via Watson-Crick base-pairing is disclosed at column 27, claim 2. Regarding claim 7 wherein the molecule of claim 1 or 2 comprises DNA or RNA is disclosed at column 5, lines 18-21.

Rejection under 35 U.S.C. 103(a): Obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Myers et al. (WO 88/05077) in view of Toole et al. (WO 92/14843) and further in view of Burke et al. (5,637,459) and Gold et al. (5,270,163). Myers et al. disclose a nucleic acid molecule comprising a vector comprising a biological effector sequence which is a nucleotide sequence encoding a polypeptide or polynucleotide and which is linked to a ligand or

"targeting factor" that has cell specific recognition or internalization-promoting properties (page 3, lines 5-13 and "Summary of the Invention"; page 4, last paragraph). The nucleotide sequence can be RNA, DNA, an antisense RNA or a DNA that expresses an antisense RNA or a protein (page 5, first full paragraph; paragraph bridging pages 5-6). The targeting factor ligand may be a protein having specific affinity for a cell surface receptor (paragraph bridging pages 6-7). See also the last paragraph of page 12 through the second full paragraph at page 14, noting that the vector includes a promoter. The claimed invention nucleic acid molecule differs from that of Myers et al. wherein the ligand or targeting factor is an aptamer. However, Toole et al. teach nucleic acid ligands or aptamers as targeting agents for delivering pharmaceuticals to desired targets (page 17, lines 5-8; page 56, lines 5-6) and that desired targets include cell surface proteins (page 18, lines 11-13). See also Gold et al. at column 32, lines 49-57. Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the nucleic acid molecule of Myers et al. with the teachings of Toole et al. to obtain the claimed invention nucleic acid molecule by substituting an aptamer for the protein targeting factor of Myers et al. because the skilled practitioner in the art would have been motivated by the obvious advantages of aptamers over proteins, e.g., as taught by Gold et al.: nucleic acids are readily synthesized and amplified *in vitro* obviating the need for cell cultures or other *in vivo* techniques and their lack of self-tolerance compared to antibodies (column 8, line 66-column 9, line 6; column 29, lines 30-34) as well as their high degree of target specificity. Other embodiments of the claimed invention molecule, particular as recited in claims 28-35 and 39-41 are disclosed by Burke et al. and Gold et al. as set forth above (paragraphs 3 and 4).

10. Claims 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferkol et al. (J. Clin. Invest. 1993) in view of Gold et al. (5,270,163). The claimed invention is a method of introducing a biological effector sequence into a cell by contacting the cell with a nucleic acid molecule of claim 1 or 2, i.e., a nucleic acid molecule comprising an aptamer covalently linked or hybridized to a biological effector sequence by contacting the nucleic acid molecule with the cell or by administering the nucleic acid molecule to an organism, i.e., gene therapy. Ferkol et al. disclose a method of introducing a biological effector

sequence (exogenous gene) into a cell (human tracheal epithelial cell) by contacting the biological effector sequence comprising an immunoglobulin fragment specific for a cell surface receptor (pIgR) with the cell (page 2397, first full paragraph). The claimed invention method differs from that of Ferkol et al. wherein the effector sequence is part of a nucleic acid molecule comprising an aptamer instead of the antibody fragment and in the embodiment of administering the biological effector sequence to an organism. However, Ferkol et al. suggest administration *in vivo* (page 37, column 2, second full paragraph) and Gold et al. teach the use of aptamers (nucleic acid ligands) as antibodies. Gold et al. further teach the use of antibody aptamers for *in vivo* applications including therapeutic methods requiring specific direction of a therapeutic agent (biological effector sequence) to a specific target site (column 29, lines 11-22). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Ferkol et al. with the teachings of Gold et al. to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success by the advantages of aptamers over conventional antibodies such as the ability to make aptamers *in vitro* rather than by immunizing animals (column 8, line 66-column 9, line 6) as well as the known low toxicity of nucleic acids and their general inertness to the immune system.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 9:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724. The examiner's Rightfax number is 703-746-3148.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)

308-0196. For questions and requests relating to formal matters contact Patent Analyst Tiffany Tabb at 703-605-1238.

Stephanie Zitomer, Ph.D.
July 8, 2002